NCI Launches Study of High-Dose Chemotherapy With Stem Cell Transplants for Ovarian Cancer

In an effort to resolve one of the ongoing controversies in cancer care, the National Cancer Institute (NCI) launched the first large national study of high-dose chemotherapy for ovarian cancer with transplantation of bone marrow blood stem cells. The study is expected to answer critical questions about the use of this intensive therapy in women with advanced ovarian cancer.

"This trial should help resolve the debate over whether high-dose chemotherapy is more, equally, or less effective compared to conventional chemotherapy," said NCI's Edward Trimble, M.D., who discussed the study at a meeting of the Gynecologic Oncology Group in Denver, Colorado in January 1997. "We also expect the trial to tell us more about the impact of this treatment on quality of life."

"I am hopeful that this study will lead us to understand more about the effectiveness of high-dose chemotherapy for advanced ovarian cancer," said Connecticut congresswoman Rosa DeLauro. "As a survivor of this particular form of cancer, I am especially grateful for the work NCI is doing to increase the survival rate for this deadly disease."

High-dose chemotherapy, which is used to kill as many cancer cells as possible, also kills a large number of healthy blood cells. As a result, this treatment is usually accompanied by the

procedure known as autologous bone marrow transplantation or, more accurately, autologous stem cell transplantation (ASCT).

ASCT uses special technology to remove stem cells, the immature cells that are destined to become blood cells, from either bone marrow or blood. After chemotherapy, the stem cells are transplanted back into the patient. The transplant enables the patient to regenerate blood cells, particularly the infection-fighting white blood cells, that have been destroyed.

The study will enroll 275 women with advanced (stage III) ovarian cancer who still have evidence of the disease after undergoing surgery and one course of chemotherapy. The women will be divided randomly into two groups. One group will receive high doses of three drugs—carboplatin, mitoxantrone, and cyclophosphamide—with ASCT. The second group will receive paclitaxel (taxol) and carboplatin, a combination now widely considered an optimal therapy for ovarian cancer at this stage.

The researchers will compare the two treatments by measuring their effect on overall survival and progression-free survival (the number of months during which no new tumor growth occurs). They will also attempt to assess any differences in quality of life, including both physical and psychological well-being, among women taking the two treatments.

The study will take place at dozens of research centers around the country, all of which are members of either the Gynecologic Oncology Group or one of several other cooperative trial groups that is NCI supported. Medical centers that belong to the cooperative trial groups conduct studies jointly and pool their data.

Ovarian cancer is the leading cause of death from all gynecologic cancer in the United States. In 1996, approximately 26,700 new cases were diagnosed and about 14,800 women died of the disease. Despite its initial responsiveness to chemotherapy, it has remained

difficult to cure. The vast majority of cases are not diagnosed until they have reached one of the later stages. Among women with stage III disease, 49 percent survive for 5 years after diagnosis.

Questions and Answers About the Ovarian Cancer High-Dose Chemotherapy Trial

The National Cancer Institute (NCI) is sponsoring the Ovarian Cancer High-Dose Chemotherapy Trial to compare two different ways of treating women with advanced ovarian cancer. The following questions and answers provide more details on the study and the procedure.

The Study

1. What is the Ovarian Cancer High-Dose Chemotherapy Trial?

The Ovarian Cancer High-Dose Chemotherapy Trial is a study designed to show whether high-dose chemotherapy with autologous stem cell transplantation (ASCT) is more, equally, or less effective than standard-dose chemotherapy in treating women with advanced ovarian cancer. The procedure involves higher-than-average doses of standard chemotherapy drugs. The high doses kill not only many cancer cells, but also many healthy blood cells. To enable the patient to grow a new supply of blood cells, her own bone marrow or blood stem cells are removed before chemotherapy and then returned afterwards (see question 11 for more details on this procedure).

2. What is a clinical trial?

A clinical trial is a study with people designed to show how a particular approach—for instance, a promising treatment or a possible way to prevent cancer—affects those who receive it. The study design is specified in a document called a protocol.

Treatment clinical trials fall into three categories.

- Phase I trials test the safety of a new treatment in a small number of patients.
- Phase II trials assess how effective a treatment is against various kinds of cancer.
- Phase III trials, which usually involve many patients in different locations, compare two or more different treatments; often phase III trials compare an established, or "standard" therapy with one that has shown promise in phase II trials.

The Ovarian Cancer High-Dose Chemotherapy Trial is a phase III trial.

3. Why is the NCI sponsoring the Ovarian Cancer High-Dose Chemotherapy Trial?

NCI expects this trial to resolve major questions about the use of high-dose chemotherapy with stem cell transplantation in ovarian cancer. The treatment is controversial because it is riskier and more expensive than more conventional treatments, while its benefits compared to other treatments are still not clear. Some earlier phase II studies suggested that this treatment may extend survival time for women with advanced ovarian cancer, while others have found it to have no significant advantage over standard-dose chemotherapy.

4. Who is eligible to take part in this trial?

Women age 65 and under who have stage III ovarian cancer—cancer that has moved beyond the ovaries to other parts of the pelvis—may be eligible for this trial if they still have evidence of disease after initial surgery and one course of chemotherapy and if their disease has been shown to be sensitive to chemotherapy. Following the first course of chemotherapy, patients must have no single tumor greater than one centimeter (less than one half of an inch) to be eligible for the study.

5. How is the study designed?

The trial will enroll about 275 women who will be divided randomly into two groups.

- One group will receive a standard therapy—the drugs paclitaxel and carboplatin—every 3 weeks over a period of about 3 months.

- The other group will receive high doses of three drugs—carboplatin, cyclophosphamide, and mitoxantrone. Because the high doses can destroy healthy blood cells as well as cancer cells, women in this group will also receive blood stem cell transplants (see question 11).

In addition, women in both groups will complete a series of questionnaires concerning changes in their quality of life at various points during and after treatment.

6. What specifically will researchers learn from this trial?

Researchers will compare the two treatments to learn 1) whether one form of treatment is associated with longer survival; 2) whether there are differences between the two groups in progression-free survival (months during which the cancer does not grow) between the two groups; 3) how the side effects of the two treatments compare, and 4) how the treatments affect the quality of life of patients. These are the principal objectives, or "endpoints," on which the researchers will collect data.

7. Why are the researchers examining quality-of-life issues in this trial?

In advanced ovarian cancer, a cure or even long-term remission is unlikely in the majority of patients, regardless of treatment. Therefore, the benefit of any treatment, such as a longer survival time, has to be weighed against the disadvantages, such as side effects.

For example, high-dose chemotherapy with stem cell transplantation might be found to extend survival time only slightly when compared to standard therapy. If at the same time the patient's quality of life deteriorated sharply, then the overall value of the treatment to the patient could become questionable.

Furthermore, progression-free survival time might be improved in the high-dose group but not overall survival. In that case, it would be important to determine whether the extended period of progression-free survival was associated with a better quality of life.

8. What quality-of-life issues will be examined and how?

Issues to be assessed include physical, social, and emotional well-being; ability to function at work and/or at home; and patients' feelings about the treatment and the health professionals with whom they see. Patients will complete quality-of-life questionnaires when they join the study, during treatment, and at 3-month intervals after entering the study and completing treatment for about 15 months.

9. Where is the trial taking place?

The trial will take place at medical centers around the country that belong to one of several NCI cooperative trial groups. The cooperative trial groups are networks of institutions and researchers who conduct studies jointly, using identical protocols and pooling their data. Institutions involved in this trial must have transplant centers that have been approved by cooperative trial groups. If a transplant center does not have cooperative trial group approval, it may be approved, on a case by case basis, by researchers in charge of this trial.

To learn more about the trial and participating institutions, patients and physicians may call the NCI's toll-free Cancer Information Service at 1–800–4–CANCER (1–800–422–6237). The TTY number is 1–800–332–8615.

10. When will the results be available?

Results could be available in the year 2003. However, the answer to this question depends on several factors, including how long it takes researchers to enroll patients in the study. NCI expects enrollment, which began in January 1997, to take about 5 years. An 18-month follow-up period is planned.

The Procedure

11. What is stem cell transplantation?

Bone marrow and blood stem cell transplants—collectively known as stem cell transplants—are used in several cancers as supportive therapy to "rescue" patients from the otherwise potentially fatal effects of treatment with high-dose chemotherapy.

Stem cells are immature blood cells that will later develop into full-fledged white and red blood cells and platelets. They are found both in bone marrow, the spongy material inside bone that produces these blood cells, and in circulating, or "peripheral," blood. Three types of stem cell transplants are used to treat cancer patients:

- ***Autologous transplantation*** is the removal of some of the patient's own healthy stem cells or bone marrow, which are then returned to the patient after treatment; it is the only form of transplant used in ovarian cancer.

- ***Allogeneic transplants*** come from people other than the patient.

- ***Syngeneic transplants*** come from a patient's identical twin.

Autologous bone marrow and peripheral stem cell transplants are often used in combination.

12. What risks and side effects are associated with high-dose chemotherapy?

The major risk of high-dose chemotherapy is an increased susceptibility to infection and bleeding, due to the destruction of infection-fighting blood cells (white blood cells) and blood cells that clot (platelets). About 3 to 5 percent of patients treated with high-dose chemotherapy die prematurely due to the effects of treatment.

As with standard doses of chemotherapy, high doses can also cause hair loss, nausea, vomiting, fatigue, loss of appetite, mouth sores, and skin reactions. Patients also may develop complications in the liver, kidneys, lungs, and/or heart, as well as other complications.

13. What is the status of high-dose chemotherapy with stem cell transplants in other cancers?

Some physicians consider high-dose chemotherapy with stem cell transplantation to be the best treatment option, under certain circumstances, for lymphoma, some types of leukemia, and neuroblastoma (an uncommon cancer that usually occurs in children). Randomized clinical trials are now under way to evaluate this treatment in breast cancer and multiple myeloma.

14. How much does the procedure cost?

Because it is a highly technical procedure that usually requires extensive hospitalization, high-dose chemotherapy with autologous stem cell transplantation is very expensive. Costs vary from place to place. According to an April 1996 report from the U.S. General Accounting Office (GAO), the procedure costs from $80,000 to $150,000 in breast cancer, compared to about $15,000 to $40,000 for conventional chemotherapy.

15. Do insurance companies provide coverage for this procedure?

Policies vary among insurance companies and other third-party payers. There are no data on how many insurers now cover high dose chemotherapy with ASCT in ovarian cancer, but the GAO report mentioned above found that an increasing number of large insurers are now covering the procedure for breast cancer. Some third-party payers may not pay for treatment received as part of a clinical trial.

Most transplant centers require a guarantee of funds in advance to cover the costs of this treatment; patients enrolling in the Ovarian Cancer High-Dose Chemotherapy Trial must have third-party coverage for treatment or other documentation of ability to pay.

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Sources of National Cancer Institute Information

Cancer Information Service

Toll-free: 1–800–4–CANCER (1–800–422–6237)
TTY (for deaf and hard of hearing callers): 1–800–332–8615

NCI Online

Internet

Use http://www.cancer.gov to reach NCI's Web site.

CancerMail Service

To obtain a contents list, send e-mail to cancermail@icicc.nci.nih.gov with the word "help" in the body of the message.

CancerFax® fax on demand service

Dial 301–402–5874 and listen to recorded instructions.

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